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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
10/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/585,964	GUAN ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-23,25,29,30 and 32-47* is/are pending in the application.

4a) Of the above claim(s) *18-23,25,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 18-23, 25, 29, 30 and 32-47 are pending.

Applicant's cancellation of claims 1-17, 24, 26-28, 31, addition of claims 32-47, and amendments to the specification as submitted in a communication filed on 6/17/2009 are acknowledged.

Claims 18-23, 25, 29-30 remain withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 18-23, 25, 29, 30 and 32-47 are at issue and are being examined herein.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The specification was objected to for having several inconsistencies throughout the specification regarding the use of sequence identifiers. In view of the amendments to the sequence listing and the drawings, this objection is hereby withdrawn.

Claim Objections

2. Claim 32 is objected to due to the recitation of "having at least 35% amino acid sequence identity with SEQ ID NO: 12 for a T7 Endo I". This should be amended to recite "having at least 35% sequence identity with the T7 Endo I of SEQ ID NO: 12". Appropriate correction is required.

3. Claims 36 and 38 are objected to due to the recitation of "further comprising (c)…". This should be amended to recite "further comprising greater/reduced DNA cleavage...". Appropriate correction is required.

4. Claim 42 objected to due to the recitation of "substitution at the PA; or a deletion of PA, Pro(P) and Ala(A)....". It should be amended to recite, for example, "or a tetrapeptide substitution; or wherein the deletion is a deletion of the PA dipeptide". Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

5. Claims 1-17, 24, 26-28, 31 were rejected and new claims 32-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This rejection as it relates to claims 1-17, 24, 26-28, 31 has been discussed at length in the Office action of 2/11/09. While the rejection is no longer applied to claims 1-17, 24, 26-28, 31 by virtue of their cancellation, this rejection is now applied to new claims 32-47 for the reasons of record and those set forth below.

7. Applicant argues that the specification discloses 9 species of the claimed genus of proteins and 24 β-bridge site mutants. Applicant further argues that (1) Example 1 describes how oligonucleotide mixtures can be used to generate the desired mutants, (2) Example 2 provides assays to analyze the generated mutants, (3) a structure/function correlation has been provided, (4) the structure of T7 Endo I is well known and studied, (5) the Conserved Domain Architecture Retrieval Tool can be used to identify members of the claimed genus, and (6) the catalytic regions and the β-bridge are clearly identifiable.

8. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of new claims 32-47. The Examiner acknowledges the teachings of the specification. However, it is noted that the claims are not limited to variants of the polypeptide of SEQ ID NO: 12 where the only modifications are in the β-bridge, or the 24 specific variants disclosed in the specification. The claims

encompass man-made mutants as well as naturally occurring proteins which have the specific structural/functional limitations recited. While it is agreed that the β-bridge can be identified, the claims require an enzyme which has reduced toxicity in *E. coli* and that can cleave nucleic acids having specific conformations. The structural features associated with that specific function have not been provided so that one could recognize which naturally-occurring or man-made mutants having the recited structural features also have the recited functional features.

The total number of variants of a polypeptide having a specific sequence identity can be calculated from the formula $N!x19^{A}/(N-A)!/A!$, where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the polypeptide of SEQ ID NO: 12 having 35% sequence identity to SEQ ID NO: 12, the total number of variants to be tested is $149!x19^{97}/(149-97)!/97!$ (SEQ ID NO: 12 has 149 amino acids; 97 amino acids = 0.65x149) or $5.3x10^{166}$ variants. The claims encompass a subgenus within this immense number of structural variants which have the recited functional limitations. However, the specification fails to disclose how to recognize those species within this immense genus which have the recited activity. Applicant's attention is directed to Example 11A of the revised Written Description Guidelines available since March 2008 for further guidance. Thus, for the reasons of record and those set forth above, one cannot reasonably conclude that the claimed invention is adequately described by the teachings of the specification.

9. Claims 1-17, 24, 26-28, 31 were rejected and new claims 32-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) variants of the single T7 endonuclease I used in Example 1 wherein said variants differ from that single T7 endonuclease I only by (1) the deletion of a Pro-Ala dipeptide in the β-bridge of that single T7 endonuclease I, or (2) by substituting a Pro-Ala dipeptide in the β-bridge of that single T7 endonuclease I with an alanine residue, (B) a kit comprising said variants, (C) a method to recombinantly produce said variants, and (D) a method

to determine whether a DNA substrate has a single nucleotide polymorphism wherein said method requires the variants of (A), does not reasonably provide enablement for (1) any protein having at least 35% sequence identity to a T7 Endonuclease I/ SEQ ID NO: 12, wherein said protein has two catalytic domains linked by a β-bridge, wherein said protein is enzymatically active and not sufficiently toxic to kill a host cell, wherein said protein has increased enzyme specificity, different activity in the presence of magnesium or manganese, an increased ratio of nicking a cruciform structure relative to double strand cleavage, an increased ratio of cleaved cruciform DNA to non-cleaved DNA, and/or reduction in nicking opposite a preexisting nick site, (2) a kit comprising said protein, (3) a method to recombinantly produce said protein, or (4) a method to determine whether a DNA substrate has a single nucleotide polymorphism wherein said method uses that protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. This rejection as it relates to claims 1-17, 24, 26-28, 31 has been discussed at length in the Office action of 2/11/09. While the rejection is no longer applied to claims 1-17, 24, 26-28, 31 by virtue of their cancellation, this rejection is now applied to new claims 32-47 for the reasons of record and those set forth below.

11. Applicant argues that (1) the present application provides working examples (Examples 1 and 2) which show how to make and test mutants, (2) the structure of the T7 Endo I is well known, and (3) applicant is the first to show that mutations in the β-bridge result in reduced toxicity and that this effect is not specific to T7 Endo I.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the teachings of the specification. However, as indicated above with regard to the written description rejection, the claims encompass a genus of proteins, man-made and naturally-occurring, having specific functional characteristics and the specification does not

provide those structural features which are associated with the recited activity. As set forth above, the total number of structural variants having at least 35% sequence identity to the polypeptide of SEQ ID NO: 12 is $5.3x10^{166}$ variants. The claims do not limit the structural variation of the polypeptide of SEQ ID NO: 12 solely to the β-bridge nor are the claims limited to structural variants of the known endonucleases of claim 40 where the only differences between the mutants and the corresponding known wild-type proteins is in the β-bridge. While applicant was able to show that at least in T7 Endo I, mutations in the β-bridge resulted in reduced toxicity, and speculates that mutations in the β-bridge of the known endonucleases recited in claim 40 could also result in reduced toxicity, there is no evidence that shows that this would be the case with any endonuclease that has a β-bridge or that the same mutations made in T7 Endo I would also result in the same reduction in toxicity in any endonuclease having a β-bridge. While methods to create variants and enzymatic assays are well known in the art, the issue in the instant case is the amount of experimentation required to enable the entire scope of the claims as the number of structural variants encompassed by the claims is immense and the specification does not provide a structure/function correlation which would allow one of skill in the art to recognize those species which are most likely to display the required activity so that the amount of testing is limited to reasonable levels. Thus, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Claim Rejections - 35 USC § 102

13. Claims 1, 13, 14, 15, 17 were rejected and new claims 32, 40, 41, 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Beck et al. (UniProt accession number P20314, February 1, 1991). This rejection has been discussed at length in the Non Final action mailed on 2/11/2009. It does not apply to claims 1, 13, 14, 15, 17 by virtue of their cancellation but is now applied to new claims 32, 40, 41, 42 for the reasons of record and those set forth below.

14. Applicant argues that Beck et al. teach the entire T3 genome and that based on the teachings of Beck et al., one would have to go through the burden of undue experimentation to deduce the claimed invention. Furthermore, applicant argues that the protein of Beck et al. is toxic to the host cell. Applicant submits that the reference of Beck et al. is not enabled.

15. Applicant's arguments have been fully considered but not found persuasive. For the record, the rejection was made on the teachings of Beck et al. as disclosed in UniProt and not on the teachings of Beck et al. as disclosed in the Journal of Molecular Biology (210:687-701, 1989). Thus, contrary to applicant's assertions, the protein of Beck et al. as disclosed in UniProt is fully enabled. New claims 32, 40-42 are directed in part to a composition comprising a protein which has two catalytic centers separated by a β-bridge, wherein said protein is at least 35% sequence identical to the polypeptide of SEQ ID NO: 12, wherein the β-bridge differs from the β-bridge of the polypeptide of SEQ ID NO: 12 by at least one amino acid, and wherein the protein is less toxic to *E. coli* compared to T7 Endo I. As previously indicated, the protein of Beck et al. is from T3 (claim 40), and has a β-bridge which differs from the β-bridge of SEQ ID NO: 12 by a substitution (PA > PE; claims 41-42). As indicated by applicant in the remarks section of the response of 6/17/2009, mutations in the β-bridge result in reduced toxicity. Therefore, since the protein of Beck et al. has a mutation in the β-bridge compared to the β-bridge of the T7 Endo I, one of skill in the art would conclude based on the remarks made by applicant that the protein of Beck et al. is less toxic than T7 Endo I. No patentable weight has been given to the term "recombinant" since this is merely a product-by-process limitation. The patentability of a product is

determined solely on its structural/functional characteristics. Therefore, the protein of Beck et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

16. Claims 24 and 31 were rejected and new claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al. (UniProt accession number P20314, February 1, 1991). This rejection has been discussed at length in the Non Final action mailed on 2/11/2009. It does not apply to claims 24 and 31 by virtue of their cancellation but is now applied to new claim 44 for the reasons of record and those set forth below.

17. Applicant argues that the claimed composition differs from the wild type T7 Endo I and as such the claimed characteristics could not be predicted from a genomic sequence of a different phage.

18. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of claim 44. For the reasons indicated above, the protein of Beck et al. is fully enabled. Furthermore, for the reasons stated above, the protein of Beck et al. meets the required structural/functional limitations recited in claim 32, 40-42. Beck et al. do not teach a kit comprising the enzyme. Claim 44 is directed in part to a kit comprising the polypeptide of claim 41. It would have been obvious to one of ordinary skill in the art at the time the invention was made to (1) make a kit which comprises the enzyme of Beck et al., a DNA substrate to test its activity, and the necessary reagents to carry out an enzymatic assay because a kit would allow all the required reagents to test enzymatic activity to be easily accessible. One of ordinary skill in the art has a reasonable expectation of success at making the kit because arranging all the required reagents in a kit is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

19. No claim is in condition for allowance.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (571) 272-0811. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
October 15, 2009